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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,060	02/12/2002	David Mu	38002-0024	2406

22907 7590 02/25/2008

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
02/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/073,060	MU ET AL.	
	Examiner	Art Unit	
	TERRA C. GIBBS	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,9,11,22,24,39,40,42,52,58-64,67-70,73,74 and 77-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,9,11,22,24,39,40,42,52,58-64,67-70,73,74 and 77-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *December 6, 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed December 6, 2007.

Claims 44, 45, 47, 53, 65, and 66 have been canceled. Claims 1, 52, and 59 have been amended.

Claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 52, 58-64, 67-70, 73, 74, and 77-82 are pending in the instant application.

Claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 52, 58-64, 67-70, 73, 74, and 77-82 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Affidavit

Applicant's Appendix 1 filed December 6, 2007 is acknowledged. The Appendix has been fully considered by the Examiner.

Information Disclosure Statement

Applicant's information disclosure statement filed December 6, 2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed September 7, 2007, claims 1, 3, 39, 44, 52, 53, 58-61, 63, 65, 67, 68, and 77-80 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is moot** against claims 44, 53, and 65 in view of Applicant's Amendment to cancel these claims filed December 6, 2007. **This rejection is withdrawn** against the other claims in view of Applicant's Amendment filed December 6, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to recite, "a method of screening". It is also noted that Applicant's amendment to the claims now has the last method step corresponding with the preamble of the claims.

In the previous Office Action mailed September 7, 2007, claims 60 and 63 were unclear over the recitation, "RT-PCR" in reference to a method for determining gene copy number. **This rejection is withdrawn** in view of Applicant's Arguments filed December 6, 2007. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Arguments that RT-PCR is used to determine an *indirect* measure of hepsin gene copy number.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed September 7, 2007, claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 44, 45, 47, 52, 53, 58-66 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection**

is moot against claims 44, 45, 47, and 53 in view of Applicant's Amendment to cancel these claims filed December 6, 2007. **This rejection is maintained against the other claims** for the reasons of record set forth in the previous Office Action mailed September 7, 2007.

Response to Arguments

In response to this rejection, Applicants argue that although the Office Action contends that the term "hepsin gene" encompasses the hepsin subfamily of genes, which the specification does not describe, the claims should be given their broadest reasonable interpretation consistent with that those skilled in the art would reach. Applicants argue that those skilled in the art would not understand the term "hepsin gene" to encompass other members of the hepsin subfamily of genes. Applicants provide Appendix 1 which shows that compared to the human hepsin protein, other hepsin subfamily genes are no more than 42% identical to hepsin. Given this disclosure, Applicants contend that it is not reasonable to conclude that the recitation of "hepsin gene" encompasses genes encoding other proteins such as those identified in Applicant's Appendix 1.

Applicant's arguments and Appendix 1 have been fully considered, but are not found persuasive because while the claims should be given their broadest reasonable interpretation consistent with that those skilled in the art would reach, the claims should also given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. Having established this, it should be noted that the

specification defines hepsin as including polymorphic variants, alleles, mutants and interspecies homologs that have substantial nucleotide homology with the nucleotide sequence as set forth in SEQ ID NO:1, which is human hepsin (see page 21, lines 12-19). Therefore, given Applicant's disclosure and considering the broadest reasonable interpretation consistent with the specification, it is the Examiner's position that those skilled in the art would consider that the recitation of "hepsin gene" to encompass genes encoding other hepsin subfamily members including those identified in Applicant's Appendix 1.

In the previous Office Action mailed September 7, 2007, claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 47, 52, 53, 58-70, 73, 74, and 77-82 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. **This rejection is moot** against claims 47, 53, 65, and 66 in view of Applicant's Amendment to cancel these claims filed December 6, 2007. **This rejection is maintained** against claims 1, 3, 9, 11, 22, 24, 39, 40, 42, 52, 58-64, 67-70, 73, 74, and 77-82 for the reasons of record set forth in the previous Office Action mailed September 7, 2007.

Response to Arguments

In response to this rejection, Applicants firstly argue that none of the reasons set forth in the previous Office Action provides a reasonable basis to doubt that the specification is enabling. For example, Applicants argue that the previous Office Action stated, "[I]t is unclear what copy number in a tumor sample is required to be considered

'amplified'", where Applicants contend that the specification contains a straightforward definition of the term "amplification".

This argument has been fully considered, but is not found persuasive because contrary to Applicant's argument, the specification does not contain a straightforward definition of the term "amplification". The specification, in the paragraph bridging pages 15 and 16 discloses:

> "The term "amplification" refers to amplification, duplication, multiplication, or multiple expression of nucleic acids or a gene, *in vivo* or *in vitro*, yielding about 2.5 fold or more copies. For example, amplification of the hepsin gene resulting in a copy number greater than or equal to 2.5 is deemed to have been amplified. However, an increase in hepsin gene copy number less than 2.5 fold can still be considered as an amplification of the gene".

As stated in the previous Office Action at page 11, first paragraph, for a gene present as two copies such as hepsin, amplification resulting in a copy number of 2.5 is not the same as a 2.5 fold amplification (the later of which would result in a gene copy number of 5). Therefore, given Applicant's definition of the term "amplification" and the fact that an increase in copy number is not equally equivalent to an increase in amplification, it is the Examiner's position that it is indeed unclear what copy number in a tumor sample is required to be considered "amplified".

Applicants secondly argue that the Office Action faults the specification because it does not provide a working example. Applicants contend that working examples are not required and given the fact that Applicant's specification teaches that hepsin gene amplification is associated with ovarian cancer, the Office Action provides no reason to

doubt that hepsin gene amplification could not be used to screen for precancerous ovarian lesions.

Applicant's arguments and contention have been fully considered, but are not found persuasive because working examples are, of course, not an absolute requirement for enablement, but are a legitimate factor in determining lack of enablement, especially when the art is of an unpredictable nature. See *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The need for additional experimentation, as in routine experimentation, is not an absolute bar to enablement, as long as the required experimentation is not undue. However, the Wands factors have been weighed and favor undue experimentation because of the lack of predictability of the art, and the specification lack of particular guidance or particular direction, undue experimentation would be required of one of skill in the art to make and use the claimed invention. For example, and as detailed in the previous Office Action mailed September 7, 2007, at page 11, the specification teaches only the analysis of tumor tissue samples, and does not provide any analysis indicating gene amplification in a precancerous lesion, as recited in the instant claims. Further, and as detailed in the previous Office Action mailed September 7, 2007, at page 11, the specification teaches only the analysis of hepsin gene copy number in various samples of primary tumor tissues and not the analysis of gene copy number in a biological subject from any non-tumor region, as encompassed by the claims. Therefore, due to the lack of particular guidance and particular direction in the specification, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

Applicants thirdly argue that the Office Action faults the specification for not providing an example of analysing hepsin gene copy number in a non-tumor tissue sample, particularly faulting the specification for not teaching whether non-tumor samples from age- and sex- matched subjects contain hepsin gene amplification. Applicants argue that, based on this point, the Office Action rejection is based on speculation and unsupported evidence that age- or sex- related hepsin gene amplification occurs.

Applicants arguments have been fully considered, but are not found persuasive because the point that the Examiner is trying to make is that Applicant's claims recite "control tissue" and "control sample" where it does not appear that the examples presented in the specification contain proper controls (e.g. non-tumor tissue). Without a proper comparison to a control, the data presented is void of any values proving statistical significance and provides no explanations as to how much amplification is seen as significant in comparison to a control.

Applicants finally argue that the previous Office Action contended that the prior art taught the "unpredictability regarding the role of hepsin in biological processes and gene association studies in general" where neither references of Lucentini or Wu are even specific for hepsin. Applicants argue that the frequency with which the hepsin gene is amplified in ovarian tumors demonstrates that detecting hepsin gene amplification can indicate the likelihood of the presence of cancer or a pre-cancerous lesion. Applicants also argue that the precise role of hepsin in ovarian, prostate, and lung cancer is not required for the skilled artisan to use amplification of the gene in

screening methods for ovarian cancers or precancerous lesions or methods of monitoring treatment efficacy for ovarian cancer or to use hepsin gene overexpression in screening methods for ovarian, prostate, or lung cancers of precancerous lesions.

Applicant's arguments have been fully considered, but are not found persuasive. First, although the references of Lucentini or Wu are not specific for hepsin, these references were relied upon to teach the overall state of the art in view of the inadequacies of the data presented in the instant specification (e.g. lack of data and unpredictability regarding hepsin gene amplification in a non-tumor sample and a lack of any data regarding the statistical significance of any results). Therefore, for the reasons set forth in the rejection of this Office Action (e.g. lack of data and unpredictability regarding hepsin gene amplification in a non-tumor sample and a lack of any data regarding the statistical significance of any results), the Examiner maintains that an undue amount of experimentation would be required to make and use the claimed invention.

Applicant's Amendment necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 67-70, 73, 74, and 77-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of claims 67, 69, 73, 77, 79, and 81 are dependent on a canceled claim. Claims 68, 70, 74, 78, 80, and 82 are dependent on claims 67, 69, 73, 77, 79, and 81, respectively. Accordingly, claims 67-70, 73, 74, and 77-82 no meaningful search can be conducted on these claims since the metes and bounds of the claims cannot be determined.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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tcg
February 17, 2008

/Sean R McGarry/

Primary Examiner, Art Unit 1635